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(54) Title: MEMBRANE-BOUND PROTEINS AND NUCLEIC ACIDS ENCODING THE SAME

(57) Abstract

The present invention is directed to polypeptides and to nucleic acid molecules encoding those polypeptides. Also provided herein are vectors and host cells comprising those nucleic acid sequences, chimeric polypeptide molecules comprising the polypeptides of the present invention fused to heterologous polypeptide sequences, antibodies which bind to the polypeptides of the present invention and to methods for producing the polypeptides of the present invention.

**NOVEL POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME****FIELD OF THE INVENTION**

The present invention relates generally to the identification and isolation of novel DNA and to the recombinant production of novel polypeptides.

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**BACKGROUND OF THE INVENTION**

Extracellular proteins play important roles in, among other things, the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells 10 and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. These secreted polypeptides or signaling molecules normally pass through the cellular secretory pathway to reach their site of action in the extracellular environment.

15 Secreted proteins have various industrial applications, including as pharmaceuticals, diagnostics, biosensors and bioreactors. Most protein drugs available at present, such as thrombolytic agents, interferons, interleukins, erythropoietins, colony stimulating factors, and various other cytokines, are secretory proteins. Their receptors, which are membrane proteins, also have potential as therapeutic or diagnostic agents. Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many efforts are 20 focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., *Proc. Natl. Acad. Sci.* 93:7108-7113 (1996); U.S. Patent No. 5,536,637].

Membrane-bound proteins and receptors can play important roles in, among other things, the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, 25 migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. Such membrane-bound proteins and cell receptors include, but are not limited to, cytokine receptors, receptor 30 kinases, receptor phosphatases, receptors involved in cell-cell interactions, and cellular adhesin molecules like selectins and integrins. For instance, transduction of signals that regulate cell growth and differentiation is regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze that process, can also act as growth factor receptors. Examples include fibroblast growth factor receptor and nerve growth factor receptor.

Membrane-bound proteins and receptor molecules have various industrial applications, including as pharmaceutical and diagnostic agents. Receptor immunoadhesins, for instance, can be employed as therapeutic agents to block receptor-ligand interactions. The membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction.

Efforts are being undertaken by both industry and academia to identify new, native receptor or membrane-bound proteins. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel receptor or membrane-bound proteins.

1. **PRO281**

A novel gene designated testis enhanced gene transcript (TEGT) has recently been identified in humans (Walter et al., Genomics 20:301-304 (1995)). Recent results have shown that TEGT protein is developmentally regulated in the mammalian testis and possesses a nuclear targeting motif that allows the protein to localize to the nucleus (Walter et al., Mamm. Genome 5:216-221 (1994)). As such, it is believed that the TEGT protein plays an important role in testis development. There is, therefore, substantial interest in identifying and characterizing novel polypeptides having homology to the TEGT protein. We herein describe the identification and characterization of novel polypeptides having homology to TEGT protein, designated herein as PRO281 polypeptides.

2. **PRO276**

Efforts are being undertaken by both industry and academia to identify new, native membrane-bound proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel membrane-bound proteins. We herein describe the identification and characterization of novel transmembrane polypeptides, designated herein as PRO276 polypeptides.

3. **PRO189**

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. We herein describe the identification and characterization of novel secreted polypeptides, designated herein as PRO189 polypeptides.

30 4. **PRO190**

Of particular interest are proteins having seven transmembrane domains (7TM), or more generally, all multiple transmembrane spanning proteins. Among multiple transmembrane spanning proteins are ion channels and transporters. Examples of transporters are the UDP-galactose transporter described in Ishida, et al., J. Biochem., 120(6):1074-1078 (1996), and the CMP-sialic acid transporter described in Eckhardt, et al., PNAS, 93(15):7572-7576 (1996). We herein describe the identification and characterization of novel transmembrane polypeptides, designated herein as PRO190 polypeptides.

**85. PRO1027**

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. We herein describe the identification and characterization of novel secreted polypeptides, designated herein as PRO1027 polypeptides.

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**86. PRO1107**

Of particular interest are novel proteins having some sequence identity to known proteins. Known proteins include PC-1, an ecto-enzyme possessing alkaline phosphodiesterase I and nucleotide pyrophosphatase activities, further described in Belli et al., *Eur. J. Biochem.*, 228(3):669-676 (1995). Phosphodiesterases are 10 also described in Fuss et al., *J. Neurosci.*, 17(23):9095-9103 (1997) and Scott et al., *Hepatology*, 25(4):995-1002 (1997). Phosphodiesterase I, is described as a novel adhesin molecule and/or cytokine (related to autotaxin) involved in oligodendrocyte function. Fuss, *supra*.

We herein describe the identification and characterization of novel polypeptides having homology nto PC-1, designated herein as PRO1107 polypeptides.

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**87. PRO1140**

Efforts are being undertaken by both industry and academia to identify new, native membrane-bound proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel membrane-bound proteins. We herein describe the identification and 20 characterization of novel transmembrane polypeptides, designated herein as PRO1140 polypeptides.

**88. PRO1106**

As the mitochondria is primarily responsible for generating energy, proteins associated with the mitochondria are of interest. Recently, a cDNA from a novel  $\text{Ca}^{++}$ -dependent member of the mitochondrial 25 solute carrier superfamily was isolated from a rabbit small intestinal cDNA library as described in Weber, et al., *PNAS USA*, 94(16):8509-8514 (1997). It was reported that this transporter has four elongation factor-hand motifs in the N-terminal and is localized in the peroxisome, although a fraction can be found in the mitochondria. Thus, this transporter, and proteins which have sequence identity to this and other members of the mitochondrial solute carrier superfamily are of particular interest.

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We herein describe the identification and characterization of novel polypeptides having homology to a peroxisomal calcium dependent solute carrier protein, designated herein as PRO1106 polypeptides.

**89. PRO1291**

Butyrophilin is a milk glycoprotein that constitutes more than 40% of the total protein associated with 35 the fat globule membrane in mammalian milk. Expression of butyrophilin mRNA has been shown to correlate with the onset of milk fat production toward the end pregnancy and is maintained throughout lactation. Butyrophilin has been identified in bovine, murine and human (see Taylor et al., *Biochim. Biophys. Acta*

1306:1-4 (1996), Ishii et al., Biochim. Biophys. Acta 1245:285-292 (1995), Mather et al., J. Dairy Sci. 76:3832-3850 (1993) and Banghart et al., J. Biol. Chem. 273:4171-4179 (1998)) and is a type I transmembrane protein that is incorporated into the fat globulin membrane. It has been suggested that butyrophilin may play a role as the principle scaffold for the assembly of a complex with xanthine dehydrogenase/oxidase and other proteins that function in the budding and release of milk-fat globules from the apical surface during lactation  
5 (Banghart et al., supra).

Given that butyrophilin plays an obviously important role in mammalian milk production, there is substantial interest in identifying novel butyrophilin homologs. We herein describe the identification and characterization of novel polypeptides having homology to butyrophilin, designated herein as PRO1291 polypeptides.

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90. **PRO1105**

Efforts are being undertaken by both industry and academia to identify new, native membrane-bound proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel membrane-bound proteins. We herein describe the identification and 15 characterization of novel transmembrane polypeptides, designated herein as PRO1105 polypeptides.

91. **PRO511**

Proteins of interest include those having sequence identity with RoBo-1, a novel member of the urokinase plasminogen activator receptor/CD59/Ly-6/snake toxin family selectively expressed in bone and 20 growth plate cartilage as described in Noel et al., J. Biol. Chem. 273(7):3878-3883 (1998). RoBo-1 is believed to play a novel role in the growth or remodeling of bone. Proteins also of interest include those having sequence identity with phospholipase inhibitors.

We herein describe the identification and characterization of novel polypeptides having homology to urokinase plasminogen activator receptors and phospholipase inhibitors, designated herein as PRO511 25 polypeptides.

92. **PRO1104**

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the 30 coding sequences for novel secreted proteins. We herein describe the identification and characterization of novel secreted polypeptides, designated herein as PRO1104 polypeptides.

93. **PRO1100**

Efforts are being undertaken by both industry and academia to identify new, native membrane-bound 35 proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel membrane-bound proteins. We herein describe the identification and characterization of novel transmembrane polypeptides, designated herein as PRO1100 polypeptides.

In another aspect, the invention concerns a PRO1140 extracellular domain comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, and most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 to X of Figure 204 (SEQ ID NO:287), wherein X is any one of amino acid residues 96 to 105 of Figure 204 (SEQ ID NO:287).

5 In yet another aspect, the invention concerns an isolated PRO1140 polypeptide, comprising the sequence of amino acid residues 1 to about 255, inclusive of Figure 204 (SEQ ID NO:287), or a fragment thereof sufficient to provide a binding site for an anti-PRO1140 antibody. Preferably, the PRO1140 fragment retains a qualitative biological activity of a native PRO1140 polypeptide.

10 In another aspect, the present invention is directed to fragments of a PRO1140 polypeptide which are sufficiently long to provide an epitope against which an antibody may be generated.

88. **PRO1106**

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence identity with a peroxisomal calcium-dependent solute carrier, wherein the polypeptide is designated in the present application 15 as "PRO1106".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1106 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO1106 polypeptide having amino acid residues 1 through 469 of Figure 206 (SEQ ID NO:289), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, 20 under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNAS59609-1470 vector deposited on June 9, 1998 with the ATCC, which includes the nucleotide sequence encoding PRO1106.

In another embodiment, the invention provides isolated PRO1106 polypeptide. In particular, the invention provides isolated native sequence PRO1106 polypeptide, which in one embodiment, includes an amino 25 acid sequence comprising residues 1 through 469 of Figure 206 (SEQ ID NO:289). Optionally, the PRO1106 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNAS59609-1470 vector deposited with the ATCC on June 9, 1998.

89. **PRO1291**

30 A cDNA clone (DNAS59610-1556) has been identified, having homology to nucleic acid encoding butyrophilin that encodes a novel polypeptide, designated in the present application as "PRO1291".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1291 polypeptide.

35 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1291 polypeptide having the sequence of amino acid residues from about 1 or about 29 to about 282, inclusive of Figure 208 (SEQ ID

NO:291), or (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1291 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 61 or about 145 and about 906, inclusive, of Figure 207 (SEQ ID NO:290). Preferably, hybridization occurs under stringent hybridization and wash conditions.

5 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209990 (DNA59610-1556) or (b) the complement of the nucleic acid molecule of (a). In a preferred embodiment, the  
10 nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209990 (DNA59610-1556).

15 In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 29 to about 282, inclusive of Figure 208 (SEQ ID NO:291), or (b) the complement of the DNA of (a).

20 In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 10 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1291 polypeptide having the sequence of amino acid residues from 1 or about 29 to about 282, inclusive of Figure 208 (SEQ ID NO:291), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80 % sequence identity, prefereably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

25 In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1291 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, and its soluble, i.e., transmembrane domain deleted or inactivated variants, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from about amino acid position 1 to about amino acid position 28 in the sequence of Figure 208 (SEQ ID NO:291). The transmembrane domain has been tentatively identified as extending from about amino acid position 258 to about amino acid  
30 position 281 in the PRO1291 amino acid sequence (Figure 208, SEQ ID NO:291).

35 In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 29 to about 282, inclusive of Figure 208 (SEQ ID NO:291), or (b) the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO1291 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length,

preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length and may be derived from the nucleotide sequence shown in Figure 207 (SEQ ID NO:290).

In another embodiment, the invention provides isolated PRO1291 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

5 In a specific aspect, the invention provides isolated native sequence PRO1291 polypeptide, which in certain embodiments, includes an amino acid sequence comprising residues 1 or about 29 to about 282 of Figure 208 (SEQ ID NO:291).

10 In another aspect, the invention concerns an isolated PRO1291 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 29 to about 282, inclusive of Figure 208 (SEQ ID NO:291).

15 In a further aspect, the invention concerns an isolated PRO1291 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 29 to about 282, inclusive of Figure 208 (SEQ ID NO:291).

20 In yet another aspect, the invention concerns an isolated PRO1291 polypeptide, comprising the sequence of amino acid residues 1 or about 29 to about 282, inclusive of Figure 208 (SEQ ID NO:291), or a fragment thereof sufficient to provide a binding site for an anti-PRO1291 antibody. Preferably, the PRO1291 fragment retains a qualitative biological activity of a native PRO1291 polypeptide.

25 20 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1291 polypeptide having the sequence of amino acid residues from about 1 or about 29 to about 282, inclusive of Figure 208 (SEQ ID NO:291), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about a 30 90% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 95% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

30 In yet another embodiment, the invention concerns agonists and antagonists of a native PRO1291 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1291 antibody.

35 In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1291 polypeptide by contacting the native PRO1291 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO1291 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

sequence of amino acid residues 1 to about 229, inclusive of Figure 306 (SEQ ID NO:424).

In a further aspect, the invention concerns an isolated PRO1384 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 to 229 of Figure 306 (SEQ ID NO:424).

5 In yet another aspect, the invention concerns an isolated PRO1384 polypeptide, comprising the sequence of amino acid residues 1 to about 229, inclusive of Figure 306 (SEQ ID NO:424), or a fragment thereof sufficient to provide a binding site for an anti-PRO1384 antibody. Preferably, the PRO1384 fragment retains a qualitative biological activity of a native PRO1384 polypeptide.

10 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1384 polypeptide having the sequence of amino acid residues from about 1 to about 229, inclusive of Figure 306 (SEQ ID NO:424), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

15 In yet another embodiment, the invention concerns agonists and antagonists of a native PRO1384 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1384 antibody.

20 In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1384 polypeptide, by contacting the native PRO1384 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

25 In a still further embodiment, the invention concerns a composition comprising a PRO1384 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

25 **136. Additional Embodiments**

In other embodiments of the present invention, the invention provides vectors comprising DNA encoding any of the above or below described polypeptides. A host cell comprising any such vector is also provided. By way of example, the host cells may be CHO cells, *E. coli*, or yeast. A process for producing any of the above or below described polypeptides is further provided and comprises culturing host cells under 30 conditions suitable for expression of the desired polypeptide and recovering the desired polypeptide from the cell culture.

35 In other embodiments, the invention provides chimeric molecules comprising any of the above or below described polypeptides fused to a heterologous polypeptide or amino acid sequence. An example of such a chimeric molecule comprises any of the above or below described polypeptides fused to an epitope tag sequence or a Fc region of an immunoglobulin.

In another embodiment, the invention provides an antibody which specifically binds to any of the above or below described polypeptides. Optionally, the antibody is a monoclonal antibody.

In yet other embodiments, the invention provides oligonucleotide probes useful for isolating genomic and cDNA nucleotide sequences, wherein those probes may be derived from any of the above or below described nucleotide sequences.

In other embodiments, the invention provides an isolated nucleic acid molecule comprising a nucleotide sequence that encodes a PRO polypeptide.

5 In one aspect, the isolated nucleic acid molecule comprises a nucleotide sequence having at least about 80% sequence identity, preferably at least about 81% sequence identity, more preferably at least about 82% sequence identity, yet more preferably at least about 83% sequence identity, yet more preferably at least about 84% sequence identity, yet more preferably at least about 85% sequence identity, yet more preferably at least about 86% sequence identity, yet more preferably at least about 87% sequence identity, yet more preferably at least about 88% sequence identity, yet more preferably at least about 89% sequence identity, yet more preferably at least about 90% sequence identity, yet more preferably at least about 91% sequence identity, yet more preferably at least about 92% sequence identity, yet more preferably at least about 93% sequence identity, yet more preferably at least about 94% sequence identity, yet more preferably at least about 95% sequence identity, yet more preferably at least about 96% sequence identity, yet more preferably at least about 97% sequence identity, yet more preferably at least about 98% sequence identity and yet more preferably at least about 99% sequence identity to (a) a DNA molecule encoding a PRO polypeptide having a full-length amino acid sequence as disclosed herein, a full-length amino acid sequence lacking the signal peptide as disclosed herein or an extracellular domain of a transmembrane protein as disclosed herein, or (b) the complement of the DNA molecule of (a).

10 In other aspects, the isolated nucleic acid molecule comprises a nucleotide sequence having at least about 80% sequence identity, preferably at least about 81% sequence identity, more preferably at least about 82% sequence identity, yet more preferably at least about 83% sequence identity, yet more preferably at least about 84% sequence identity, yet more preferably at least about 85% sequence identity, yet more preferably at least about 86% sequence identity, yet more preferably at least about 87% sequence identity, yet more preferably at least about 88% sequence identity, yet more preferably at least about 89% sequence identity, yet more preferably at least about 90% sequence identity, yet more preferably at least about 91% sequence identity, yet more preferably at least about 92% sequence identity, yet more preferably at least about 93% sequence identity, yet more preferably at least about 94% sequence identity, yet more preferably at least about 95% sequence identity, yet more preferably at least about 96% sequence identity, yet more preferably at least about 97% sequence identity, yet more preferably at least about 98% sequence identity and yet more preferably at least about 99% sequence identity to (a) a DNA molecule having the coding sequence of a full-length PRO polypeptide cDNA as disclosed herein, the coding sequence of a full-length PRO polypeptide lacking the signal peptide as disclosed herein or the coding sequence of an extracellular domain of a transmembrane PRO polypeptide as disclosed herein, or (b) the complement of the DNA molecule of (a).

15 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising a nucleotide sequence having at least about 80% sequence identity, preferably at least about 81% sequence identity, more preferably at least about 82% sequence identity, yet more preferably at least about 83% sequence identity,

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identity, yet more preferably at least about 84% sequence identity, yet more preferably at least about 85% sequence identity, yet more preferably at least about 86% sequence identity, yet more preferably at least about 87% sequence identity, yet more preferably at least about 88% sequence identity, yet more preferably at least about 89% sequence identity, yet more preferably at least about 90% sequence identity, yet more preferably at least about 91% sequence identity, yet more preferably at least about 92% sequence identity, yet more preferably at least about 93% sequence identity, yet more preferably at least about 94% sequence identity, yet more preferably at least about 95% sequence identity, yet more preferably at least about 96% sequence identity, yet more preferably at least about 97% sequence identity, yet more preferably at least about 98% sequence identity and yet more preferably at least about 99% sequence identity to (a) a DNA molecule that encodes the same mature polypeptide encoded by any of the human protein cDNAs deposited with the ATCC as disclosed herein,  
5 or (b) the complement of the DNA molecule of (a).

Another aspect the invention provides an isolated nucleic acid molecule comprising a nucleotide sequence encoding a PRO polypeptide which is either transmembrane domain-deleted or transmembrane domain-inactivated, or is complementary to such encoding nucleotide sequence, wherein the transmembrane domain(s) of such polypeptide are disclosed herein. Therefore, soluble extracellular domains of the herein described PRO  
10 polypeptides are contemplated.

Another embodiment is directed to fragments of a PRO polypeptide coding sequence that may find use as, for example, hybridization probes or for encoding fragments of a PRO polypeptide that may optionally encode a polypeptide comprising a binding site for an anti-PRO antibody. Such nucleic acid fragments are usually at least about 20 nucleotides in length, preferably at least about 30 nucleotides in length, more preferably at least about 40 nucleotides in length, yet more preferably at least about 50 nucleotides in length, yet more preferably at least about 60 nucleotides in length, yet more preferably at least about 70 nucleotides in length, yet more preferably at least about 80 nucleotides in length, yet more preferably at least about 90 nucleotides in length, yet more preferably at least about 100 nucleotides in length, yet more preferably at least about 110 nucleotides in length, yet more preferably at least about 120 nucleotides in length, yet more preferably at least  
15 about 130 nucleotides in length, yet more preferably at least about 140 nucleotides in length, yet more preferably at least about 150 nucleotides in length, yet more preferably at least about 160 nucleotides in length, yet more preferably at least about 170 nucleotides in length, yet more preferably at least about 180 nucleotides in length, yet more preferably at least about 190 nucleotides in length, yet more preferably at least about 200 nucleotides in length, yet more preferably at least about 250 nucleotides in length, yet more preferably at least about 300  
20 nucleotides in length, yet more preferably at least about 350 nucleotides in length, yet more preferably at least about 400 nucleotides in length, yet more preferably at least about 450 nucleotides in length, yet more preferably at least about 500 nucleotides in length, yet more preferably at least about 600 nucleotides in length, yet more preferably at least about 700 nucleotides in length, yet more preferably at least about 800 nucleotides in length, yet more preferably at least about 900 nucleotides in length and yet more preferably at least about 1000  
25 nucleotides in length, wherein in this context the term "about" means the referenced nucleotide sequence length plus or minus 10% of that referenced length. It is noted that novel fragments of a PRO polypeptide-encoding nucleotide sequence may be determined in a routine manner by aligning the PRO polypeptide-encoding nucleotide  
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sequence with other known nucleotide sequences using any of a number of well known sequence alignment programs and determining which PRO polypeptide-encoding nucleotide sequence fragment(s) are novel. All of such PRO polypeptide-encoding nucleotide sequences are contemplated herein. Also contemplated are the PRO polypeptide fragments encoded by these nucleotide molecule fragments, preferably those PRO polypeptide fragments that comprise a binding site for an anti-PRO antibody.

5 In another embodiment, the invention provides isolated PRO polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a certain aspect, the invention concerns an isolated PRO polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 81% sequence identity, more preferably at least about 82% sequence identity, yet more preferably at least about 83% sequence identity, yet 10 more preferably at least about 84% sequence identity, yet more preferably at least about 85% sequence identity, yet more preferably at least about 86% sequence identity, yet more preferably at least about 87% sequence identity, yet more preferably at least about 88% sequence identity, yet more preferably at least about 89% sequence identity, yet more preferably at least about 90% sequence identity, yet more preferably at least about 91% sequence identity, yet more preferably at least about 92% sequence identity, yet more preferably at least 15 about 93% sequence identity, yet more preferably at least about 94% sequence identity, yet more preferably at least about 95% sequence identity, yet more preferably at least about 96% sequence identity, yet more preferably at least about 97% sequence identity, yet more preferably at least about 98% sequence identity and yet more preferably at least about 99% sequence identity to a PRO polypeptide having a full-length amino acid sequence as disclosed herein, a full-length amino acid sequence lacking the signal peptide as disclosed herein or an 20 extracellular domain of a transmembrane protein as disclosed herein.

In a further aspect, the invention concerns an isolated PRO polypeptide comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 81% sequence identity, more preferably at least about 82% sequence identity, yet more preferably at least about 83% sequence identity, yet more preferably at least about 84% sequence identity, yet more preferably at least about 85% sequence identity, yet 25 more preferably at least about 86% sequence identity, yet more preferably at least about 87% sequence identity, yet more preferably at least about 88% sequence identity, yet more preferably at least about 89% sequence identity, yet more preferably at least about 90% sequence identity, yet more preferably at least about 91% sequence identity, yet more preferably at least about 92% sequence identity, yet more preferably at least about 93% sequence identity, yet more preferably at least about 94% sequence identity, yet more preferably at least 30 about 95% sequence identity, yet more preferably at least about 96% sequence identity, yet more preferably at least about 97% sequence identity, yet more preferably at least about 98% sequence identity and yet more preferably at least about 99% sequence identity to an amino acid sequence encoded by any of the human protein cDNAs deposited with the ATCC as disclosed herein.

In a further aspect, the invention concerns an isolated PRO polypeptide comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 81% positives, more preferably at least about 82% positives, yet more preferably at least about 83% positives, yet more preferably at least about 84% positives, yet more preferably at least about 85% positives, yet more preferably at least about 86% positives,

yet more preferably at least about 87% positives, yet more preferably at least about 88% positives, yet more preferably at least about 89% positives, yet more preferably at least about 90% positives, yet more preferably at least about 91% positives, yet more preferably at least about 92% positives, yet more preferably at least about 93% positives, yet more preferably at least about 94% positives, yet more preferably at least about 95% positives, yet more preferably at least about 96% positives, yet more preferably at least about 97% positives,  
5 yet more preferably at least about 98% positives and yet more preferably at least about 99% positives when compared with the amino acid sequence of a PRO polypeptide having a full-length amino acid sequence as disclosed herein, a full-length amino acid sequence lacking the signal peptide as disclosed herein or an extracellular domain of a transmembrane protein as disclosed herein.

In a specific aspect, the invention provides an isolated PRO polypeptide without the N-terminal signal  
10 sequence and/or the initiating methionine and is encoded by a nucleotide sequence that encodes such an amino acid sequence as hereinbefore described. Processes for producing the same are also herein described, wherein those processes comprise culturing a host cell comprising a vector which comprises the appropriate encoding nucleic acid molecule under conditions suitable for expression of the PRO polypeptide and recovering the PRO polypeptide from the cell culture.

15 Another aspect the invention provides an isolated PRO polypeptide which is either transmembrane domain-deleted or transmembrane domain-inactivated. Processes for producing the same are also herein described, wherein those processes comprise culturing a host cell comprising a vector which comprises the appropriate encoding nucleic acid molecule under conditions suitable for expression of the PRO polypeptide and recovering the PRO polypeptide from the cell culture.

20 Another embodiment of the present invention is directed to the use of a PRO polypeptide, or an agonist or antagonist thereof as hereinbefore described, or an anti-PRO antibody, for the preparation of a medicament useful in the treatment of a condition which is responsive to the PRO polypeptide, an agonist or antagonist thereof or an anti-PRO antibody.

25

#### BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a nucleotide sequence (SEQ ID NO:1) of a native sequence PRO281 (UNQ244) cDNA, wherein SEQ ID NO:1 is a clone designated herein as "DNA16422-1209".

Figure 2 shows the amino acid sequence (SEQ ID NO:2) derived from the coding sequence of SEQ ID NO:1 shown in Figure 1.

30

Figure 3 shows a nucleotide sequence (SEQ ID NO:5) of a native sequence PRO276 (UNQ243) cDNA, wherein SEQ ID NO:5 is a clone designated herein as "DNA16435-1208".

Figure 4 shows the amino acid sequence (SEQ ID NO:6) derived from the coding sequence of SEQ ID NO:5 shown in Figure 3.

35

Figure 5 shows a nucleotide sequence (SEQ ID NO:7) of a native sequence PRO189 (UNQ163) cDNA, wherein SEQ ID NO:7 is a clone designated herein as "DNA21642-1391".

Figure 6 shows the amino acid sequence (SEQ ID NO:8) derived from the coding sequence of SEQ ID NO:7 shown in Figure 5.

Figure 192 shows the amino acid sequence (SEQ ID NO:274) derived from the coding sequence of SEQ ID NO:273 shown in Figure 191.

Figure 193 shows a nucleotide sequence (SEQ ID NO:275) of a native sequence PRO1139 (UNQ577) cDNA, wherein SEQ ID NO:275 is a clone designated herein as "DNA59497-1496".

Figure 194 shows the amino acid sequence (SEQ ID NO:276) derived from the coding sequence of SEQ 5 ID NO:275 shown in Figure 193.

Figure 195 shows a nucleotide sequence (SEQ ID NO:277) of a native sequence PRO1309 (UNQ675) cDNA, wherein SEQ ID NO:277 is a clone designated herein as "DNA59588-1571".

Figure 196 shows the amino acid sequence (SEQ ID NO:278) derived from the coding sequence of SEQ ID NO:277 shown in Figure 195.

10 Figure 197 shows a nucleotide sequence (SEQ ID NO:280) of a native sequence PRO1028 (UNQ513) cDNA, wherein SEQ ID NO:280 is a clone designated herein as "DNA59603-1419".

Figure 198 shows the amino acid sequence (SEQ ID NO:281) derived from the coding sequence of SEQ ID NO:280 shown in Figure 197.

15 Figure 199 shows a nucleotide sequence (SEQ ID NO:282) of a native sequence PRO1027 (UNQ512) cDNA, wherein SEQ ID NO:282 is a clone designated herein as "DNA59605-1418".

Figure 200 shows the amino acid sequence (SEQ ID NO:283) derived from the coding sequence of SEQ ID NO:282 shown in Figure 199.

Figure 201 shows a nucleotide sequence (SEQ ID NO:284) of a native sequence PRO1107 (UNQ550) cDNA, wherein SEQ ID NO:284 is a clone designated herein as "DNA59606-1471".

20 Figure 202 shows the amino acid sequence (SEQ ID NO:285) derived from the coding sequence of SEQ ID NO:284 shown in Figure 201.

Figure 203 shows a nucleotide sequence (SEQ ID NO:286) of a native sequence PRO1140 (UNQ578) cDNA, wherein SEQ ID NO:286 is a clone designated herein as "DNA59607-1497".

25 Figure 204 shows the amino acid sequence (SEQ ID NO:287) derived from the coding sequence of SEQ ID NO:286 shown in Figure 203.

Figure 205 shows a nucleotide sequence (SEQ ID NO:288) of a native sequence PRO1106 (UNQ549) cDNA, wherein SEQ ID NO:288 is a clone designated herein as "DNA59609-1470".

Figure 206 shows the amino acid sequence (SEQ ID NO:289) derived from the coding sequence of SEQ ID NO:288 shown in Figure 205.

30 Figure 207 shows a nucleotide sequence (SEQ ID NO:290) of a native sequence PRO1291 (UNQ659) cDNA, wherein SEQ ID NO:290 is a clone designated herein as "DNA59610-1556".

Figure 208 shows the amino acid sequence (SEQ ID NO:291) derived from the coding sequence of SEQ ID NO:290 shown in Figure 207.

35 Figure 209 shows a nucleotide sequence (SEQ ID NO:292) of a native sequence PRO1105 (UNQ548) cDNA, wherein SEQ ID NO:292 is a clone designated herein as "DNA59612-1466".

Figure 210 shows the amino acid sequence (SEQ ID NO:293) derived from the coding sequence of SEQ ID NO:292 shown in Figure 209.

**85. Full-length PRO1027 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1027. In particular, Applicants have identified and isolated cDNA 5 encoding a PRO1027 polypeptide, as disclosed in further detail in the Examples below. The PRO1027-encoding clone was identified in a human uterine cervical tissue library. To Applicants present knowledge, the DNA59605-1418 nucleotide sequence encodes a novel factor.

**86. Full-length PRO1107 Polypeptides**

10 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1107. In particular, Applicants have identified and isolated cDNA encoding a PRO1107 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO1107 polypeptide has some similarity to the PC-1 protein, human insulin receptor tyrosine kinase inhibitor, an alkaline phosphodiesterase, 15 and autotaxin. Accordingly, it is presently believed that PRO1107 polypeptide disclosed in the present application is a newly identified member of the phosphodiesterase family.

**87. Full-length PRO1140 Polypeptides**

20 The present invention provides newly identified and isolated nucleotide sequences encoding novel multi-span transmembrane polypeptides referred to in the present application as PRO1140. In particular, Applicants have identified and isolated cDNA encoding a PRO1140 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, some sequence identity with known proteins was found.

**25 88. Full-length PRO1106 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1106. In particular, Applicants have identified and isolated cDNA 30 encoding a PRO1106 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO1106 polypeptide has significant similarity to the peroxisomal calcium-dependent solute carrier. Accordingly, it is presently believed that PRO1106 polypeptide disclosed in the present application is a newly identified member of the mitochondrial carrier superfamily and possesses transporter activity typical of this family.

**89. Full-length PRO1291 Polypeptides**

35 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1291. In particular, cDNA encoding a PRO1291 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

Using the WU-BLAST2 sequence alignment computer program, it has been found that a full-length native sequence PRO1291 (shown in Figure 208 and SEQ ID NO:291) has certain amino acid sequence identity with the butyrophilin protein. Accordingly, it is presently believed that PRO1291 disclosed in the present application is a newly identified butyrophilin homolog and may possess activity typical of that protein.

5

#### **90. Full-length PRO1105 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1105. In particular, Applicants have identified cDNA encoding a PRO1105 polypeptide, as disclosed in further detail in the Examples below. To Applicants present knowledge, the DNA59612-1466 nucleotide sequence encodes a novel factor. There is, however, some sequence identity 10 with a peroxydase precursor designated in a Dayhoff database as "ATTS1623\_1".

#### **91. Full-length PRO511 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO511. In particular, Applicants have identified and isolated cDNA 15 encoding a PRO511 polypeptide, as disclosed in further detail in the Examples below. The PRO511-encoding clone was isolated from a human colon tissue library. To Applicants present knowledge, the DNA59613-1417 nucleotide sequence encodes a novel factor; using BLAST and FastA sequence alignment computer programs, sequence identities with RoBo-1, phospholipase inhibitors and a protein designated as "SSC20F10\_1" were revealed, indicated that PRO511 may be related to one or more of these proteins.

20

#### **92. Full-length PRO1104 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1104. In particular, Applicants have identified and isolated cDNA 25 encoding a PRO1104 polypeptide, as disclosed in further detail in the Examples below. To Applicants present knowledge, the DNA59616-1465 nucleotide sequence encodes a novel factor; using BLAST and FastA sequence alignment computer programs, some sequence identity appeared with proteins designated as "AB002107\_1", "AF022991\_1" and "SP96\_DICDI".

#### **93. Full-length PRO1100 Polypeptides**

30

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1100. In particular, Applicants have identified cDNA encoding a PRO1100 polypeptide, as disclosed in further detail in the Examples below. To Applicants present knowledge, the DNA59619-1464 nucleotide sequence encodes a novel factor; using BLAST and FastA sequence alignment computer programs, only some sequence identity with known proteins was revealed. There is some sequence 35 identity with the yeast hypothetical 42.5 KD protein in TSM1-ARE1 intergenic region (ACCESSION NO:140496), designated "YSCT4\_YEAST".

may be a novel transporter. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced sequence identity between the PRO1106 amino acid sequence and at least the following Dayhoff sequences, AF004161\_1, IG002N01\_25, GDC\_BOVIN and BT1\_MAIZE.

EXAMPLE 92: Isolation of cDNA clones Encoding Human PRO1291

5        Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database, designated 120480. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LifeSeq®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul  
10 et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56425.

15      In light of an observed sequence homology between the DNA56425 sequence and an EST sequence encompassed within the Incyte EST clone no. 2798803, the Incyte EST clone 2798803 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 207 and is herein designated as DNA59610-1556.

20      Clone DNA59610-1556 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 61-63 and ending at the stop codon at nucleotide positions 907-909 (Figure 207). The predicted polypeptide precursor is 282 amino acids long (Figure 208). The full-length PRO1291 protein shown in Figure 208 has an estimated molecular weight of about 30,878 daltons and a pI of about 5.27. Analysis of the full-length PRO1291 sequence shown in Figure 208 (SEQ ID NO:291) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 28, a transmembrane domain from about amino acid 258 to about amino acid 281 and potential N-glycosylation sites from about amino acid 112 to about  
25 amino acid 115, from about amino acid 160 to about amino acid 163, from about amino acid 190 to about amino acid 193, from about amino acid 196 to about amino acid 199, from about amino acid 205 to about amino acid 208, from about amino acid 216 to about amino acid 219 and from about amino acid 220 to about amino acid 223.. Clone DNA59610-1556 has been deposited with ATCC on June 16, 1998 and is assigned ATCC deposit no. 209990.

30      An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 208 (SEQ ID NO:291), evidenced significant homology between the PRO1291 amino acid sequence and the following Dayhoff sequences: HSU90552\_1, HSU90144\_1, AF033107\_1, HSB73\_1, HSU90142\_1, GGCD80\_1, P\_W34452, MOG\_MOUSE, B39371 and P\_R71360.

Deposit of Material

The following materials have been deposited with the American Type Culture Collection, 10801 University Blvd., Manassas, VA 20110-2209, USA (ATCC):

Table 2

	<u>Material</u>	<u>ATCC Dep. No.</u>	<u>Deposit Date</u>
5	DNA16422-1209	209929	June 2, 1998
	DNA16435-1208	209930	June 2, 1998
	DNA21624-1391	209917	June 2, 1998
	DNA23334-1392	209918	June 2, 1998
10	DNA26288-1239	209792	April 21, 1998
	DNA26843-1389	203099	August 4, 1998
	DNA26844-1394	209926	June 2, 1998
	DNA30862-1396	209920	June 2, 1998
	DNA35680-1212	209790	April 21, 1998
15	DNA40621-1440	209922	June 2, 1998
	DNA44161-1434	209907	May 27, 1998
	DNA44694-1500	203114	August 11, 1998
	DNA45495-1550	203156	August 25, 1998
	DNA47361-1154	209431	November 7, 1997
20	DNA47394-1572	203109	August 11, 1998
	DNA48320-1433	209904	May 27, 1998
	DNA48334-1435	209924	June 2, 1998
	DNA48606-1479	203040	July 1, 1998
	DNA49141-1431	203003	June 23, 1998
25	DNA49142-1430	203002	June 23, 1998
	DNA49143-1429	203013	June 23, 1998
	DNA49647-1398	209919	June 2, 1998
	DNA49819-1439	209931	June 2, 1998
	DNA49820-1427	209932	June 2, 1998
30	DNA49821-1562	209981	June 16, 1998
	DNA52192-1369	203042	July 1, 1998
	DNA52598-1518	203107	August 11, 1998
	DNA53913-1490	203162	August 25, 1998
	DNA53978-1443	209983	June 16, 1998
35	DNA53996-1442	209921	June 2, 1998
	DNA56041-1416	203012	June 23, 1998
	DNA56047-1456	209948	June 9, 1998
	DNA56050-1455	203011	June 23, 1998
	DNA56110-1437	203113	August 11, 1998
40	DNA56113-1378	203049	July 1, 1998
	DNA56410-1414	209923	June 2, 1998
	DNA56436-1448	209902	May 27, 1998
	DNA56855-1447	203004	June 23, 1998
	DNA56859-1445	203019	June 23, 1998
45	DNA56860-1510	209952	June 9, 1998
	DNA56865-1491	203022	June 23, 1998
	DNA56866-1342	203023	June 23, 1998
	DNA56868-1209	203024	June 23, 1998
	DNA56869-1545	203161	August 25, 1998
50	DNA56870-1492	209925	June 2, 1998
	DNA57033-1403	209905	May 27, 1998
	DNA57037-1444	209903	May 27, 1998
	DNA57129-1413	209977	June 16, 1998

	DNA57690-1374	209950	June 9, 1998
	DNA57693-1424	203008	June 23, 1998
	DNA57694-1341	203017	June 23, 1998
	DNA57695-1340	203006	June 23, 1998
	DNA57699-1412	203020	June 23, 1998
5	DNA57702-1476	209951	June 9, 1998
	DNA57704-1452	209953	June 9, 1998
	DNA57708-1411	203021	June 23, 1998
	DNA57710-1451	203048	July 1, 1998
	DNA57711-1501	203047	July 1, 1998
10	DNA57827-1493	203045	July 1, 1998
	DNA57834-1339	209954	June 9, 1998
	DNA57836-1338	203025	June 23, 1998
	DNA57838-1337	203014	June 23, 1998
	DNA57844-1410	203010	June 23, 1998
15	DNA58721-1475	203110	August 11, 1998
	DNA58723-1588	203133	August 18, 1998
	DNA58737-1473	203136	August 18, 1998
	DNA58743-1609	203154	August 25, 1998
	DNA58846-1409	209957	June 9, 1998
20	DNA58848-1472	209955	June 9, 1998
	DNA58849-1494	209958	June 9, 1998
	DNA58850-1495	209956	June 9, 1998
	DNA58853-1423	203016	June 23, 1998
	DNA58855-1422	203018	June 23, 1998
25	DNA59205-1421	203009	June 23, 1998
	DNA59211-1450	209960	June 9, 1998
	DNA59213-1487	209959	June 9, 1998
	DNA59214-1449	203046	July 1, 1998
	DNA59215-1425	209961	June 9, 1998
30	DNA59220-1514	209962	June 9, 1998
	DNA59488-1603	203157	August 25, 1998
	DNA59493-1420	203050	July 1, 1998
	DNA59497-1496	209941	June 4, 1998
	DNA59588-1571	203106	August 11, 1998
35	DNA59603-1419	209944	June 9, 1998
	DNA59605-1418	203005	June 23, 1998
	DNA59606-1471	209945	June 9, 1998
	DNA59607-1497	209957	June 9, 1998
	DNA59609-1470	209963	June 9, 1998
40	DNA59610-1559	209990	June 16, 1998
	DNA59612-1466	209947	June 9, 1998
	DNA59613-1417	203007	June 23, 1998
	DNA59616-1465	209991	June 16, 1998
	DNA59619-1464	203041	July 1, 1998
45	DNA59620-1463	209989	June 16, 1998
	DNA59625-1498	209992	June 17, 1998
	DNA59767-1489	203108	August 11, 1998
	DNA59776-1600	203128	August 18, 1998
	DNA59777-1480	203111	August 11, 1998
50	DNA59820-1549	203129	August 18, 1998
	DNA59827-1426	203089	August 4, 1998
	DNA59828-1608	203158	August 25, 1998
	DNA59838-1462	209976	June 16, 1998
	DNA59839-1461	209988	June 16, 1998
55	DNA59841-1460	203044	July 1, 1998
	DNA59842-1502	209982	June 16, 1998

	DNA59846-1503	209978	June 16, 1998
	DNA59847-1511	203098	August 4, 1998
	DNA59848-1512	203088	August 4, 1998
	DNA59849-1504	209986	June 16, 1998
	DNA59853-1505	209985	June 16, 1998
5	DNA59854-1459	209974	June 16, 1998
	DNA60283-1484	203043	July 1, 1998
	DNA60615-1483	209980	June 16, 1998
	DNA60619-1482	209993	June 16, 1998
	DNA60621-1516	203091	August 4, 1998
10	DNA60622-1525	203090	August 4, 1998
	DNA60625-1507	209975	June 16, 1998
	DNA60627-1508	203092	August 4, 1998
	DNA60629-1481	209979	June 16, 1998
	DNA61755-1554	203112	August 11, 1998
15	DNA61873-1574	203132	August 18, 1998
	DNA62814-1521	203093	August 4, 1998
	DNA62872-1509	203100	August 4, 1998
	DNA62876-1517	203095	August 4, 1998
	DNA62881-1515	203096	August 4, 1998
20	DNA64852-1589	203127	August 18, 1998
	DNA64884-1527	203155	August 25, 1998
	DNA64890-1612	203131	August 18, 1998
	DNA65412-1523	203094	August 4, 1998
	DNA66308-1537	203159	August 25, 1998
25	DNA66309-1538	203235	September 15, 1998
	DNA67004-1614	203115	August 11, 1998
	DNA68869-1610	203164	August 25, 1998
	DNA68872-1620	203160	August 25, 1998
	DNA71159-1617	203135	August 18, 1998
30			

These deposit were made under the provisions of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure and the Regulations thereunder (Budapest Treaty). This assures maintenance of a viable culture of the deposit for 30 years from the date of deposit. The deposits will be made available by ATCC under the terms of the Budapest Treaty, and subject to an agreement

35 between Genentech, Inc. and ATCC, which assures permanent and unrestricted availability of the progeny of the culture of the deposit to the public upon issuance of the pertinent U.S. patent or upon laying open to the public of any U.S. or foreign patent application, whichever comes first, and assures availability of the progeny to one determined by the U.S. Commissioner of Patents and Trademarks to be entitled thereto according to 35 USC §122 and the Commissioner's rules pursuant thereto (including 37 CFR §1.14 with particular reference to

40 886 OG 638).

The assignee of the present application has agreed that if a culture of the materials on deposit should die or be lost or destroyed when cultivated under suitable conditions, the materials will be promptly replaced on notification with another of the same. Availability of the deposited material is not to be construed as a license to practice the invention in contravention of the rights granted under the authority of any government in accordance with its patent laws.

45 The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The present invention is not to be limited in scope by the construct deposited, since the

deposited embodiment is intended as a single illustration of certain aspects of the invention and any constructs that are functionally equivalent are within the scope of this invention. The deposit of material herein does not constitute an admission that the written description herein contained is inadequate to enable the practice of any aspect of the invention, including the best mode thereof, nor is it to be construed as limiting the scope of the claims to the specific illustrations that it represents. Indeed, various modifications of the invention in addition 5 to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims.

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## FIGURE 207

GGAAGGCAGCGGCAGCTCCACTCAGCCAGTACCCAGATA CGCTGGAACCTTCCCCAGCCAT  
GGCTTCCCTGGGGCAGATCCTCTGGAGCATAATTAGCATCATCATTATTCTGGCTGGAG  
CAATTGCACTCATCATTGGCTTGGTATTCAGGGAGACACTCCATCACAGTCACTACTGTC  
GCCTCAGCTGGGAACATGGGGAGGATGGAATCCTGAGCTGCACCTTGAAACCTGACATCAA  
ACTTTCTGATATCGTGTACAATGGCTGAAGGAAGGTGTTAGGCTTGGTCATGAGTTCA  
AAGAAGGCAAAGATGAGCTGCGAGCAGGATGAAATGTTAGGCTGGGACAGCAGTGTGTT  
GCTGATCAAGTGTAGTTGGCAATGCCCTTGGCTGAAAAACGTGCAACTCACAGATGC  
TGGCACCTACAAATGTTATATCATCACTCTAAAGGCAAGGGAAATGCTAACCTTGAGTATA  
AAACTGGAGCCTTCAGCATGCCGAAGTGAATGTGGACTATAATGCCAGCTCAGAGACCTTG  
CGGTGTGAGGCTCCCCGATGGTCCCCCAGCCCACAGTGGCTGGCATCCCAAGTTGACCA  
GGGAGCCAACCTCTCGGAAGTCTCCAATACCAGCTTGAGCTGAACTCTGAGAATGTGACCA  
TGAAGGTTGTCTGTGCTCTACAATGTTACGATCAACAACACATACTCCTGTATGATTGAA  
AATGACATTGCCAAAGCAACAGGGATATCAAAGTGACAGAAATCGGAGATCAAAAGGCGGAG  
TCACCTACAGCTGCTAAACTCAAAGGCTCTGTGTCTCTTCTTGCCTCAGCT  
GGGCACTCTGCCCTCTGCCCTTACCTGATGCTAAAATTGTGCCTGGCCACAAAAAAG  
CATGCAAAGTCATTGTTACAACAGGGATCTACAGAACTATTCACCACAGATATGACCTAG  
TTTATATTCTGGGAGGAAATGAATTCTAGTAGAAGTCTGGAGTGAGCAAACAAGAGCA  
AGAAACAAAAAGAAGCCAAAGCAGAAGGCTCCAATATGAACAAAGATAATCTATCTCAA  
GACATATTAGAAGTTGGAAAATAATTCTAGTGAACTAGACAAGTGTGTTAAGAGTGATAAG  
TAAAATGCACGTGGAGACAAGTGCATCCCCAGATCTCAGGGACCTCCCCCTGCCTGTCACCT  
GGGAGTGAGAGGACAGGATAGTGCATGTTCTTGCTCTGAATTTAGTTATATGTGCTG  
TAATGTTGCTCTGAGGAAGCCCTGGAAAGTCTATCCAAACATATCCACATCTTATATTCCA  
CAAATTAAGCTGTAGTATGTACCTAACGCTGCTAATTGACTGCCACTCGCAACTCAGG  
GGCGGCTGCATTTAGTAATGGGCAAATGATTCACTTTATGATGCTTCAAAGGTGCCT  
TGGCTCTTCCAACTGACAAATGCCAAAGTTGAGAAAATGATCATAATTTAGCATAAA  
ACAGAGCAGTCGGGACACCGATTATAAAACTGAGCACCTTCTTTAAACAAAAAA  
AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

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## FIGURE 208

MASLGQILFWIISIIILAGAIALIIGFGISGRHSITVTTVASAGNIGEDGILSCTFEPDI  
KLSDIVIQWLKEGVGLVHEFKEGKDELSEQDEMFRGRTAVFADQVIVGNASLRKNVQLTD  
AGTYKCYIITSKGKGNANLEYKTGAFSMPEVNVDYNASSETLRCEAPRWFPQPTVVWASQVD  
QGANFSEVSNTSFELNSENVTMKVSVLYNVTINNTYSCMIENDIAKATGDIKVTESEIKRR  
SHLQLLN SKASLCVSSFFAISWALLPLSPYLMK